Clinical Analysis of Adverse Drug Reactions

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Epidemiology of ADRs

- substantial morbidity and mortality
- estimates of incidence vary with study methods, population, and ADR definition
- 4th to 6th leading cause of death among hospitalized patients*
- 6.7% incidence of serious ADRs*
- 0.3% to 7% of all hospital admissions
- annual dollar costs in the billions
- 30% to 60% are preventable

*JAMA. 1998;279:1200-1205.

Definitions

- WHO
  - response to a drug that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function
  - excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

Definitions

- FDA (serious adverse reactions)
  - Result in death
  - Life-threatening
  - Require hospitalization
  - Prolong hospitalization
  - Cause disability
  - Cause congenital anomalies
  - Require intervention to prevent permanent injury

Classification

- Onset of event:
  - Acute
    - » within 60 minutes
  - Sub-acute
    - » 1 to 24 hours
  - Latent
    - » > 2 days

Classification

- Severity of reaction:
  - Mild
    - » bothersome but requires no change in therapy
  - Moderate
    - » requires change in therapy, additional treatment, hospitalization
  - Severe
    - » disabling or life-threatening

Classification

- Type A
  - » extension of pharmacologic effect
  - » often predictable and dose dependent
  - » responsible for at least two-thirds of ADRs
  - » e.g., propranolol and heart block, anticholinergics and dry mouth
- Type B
  - » idiosyncratic or immunologic reactions
  - » rare and unpredictable
  - » e.g., chloramphenicol and aplastic anemia

Classification

- Type C
  - » associated with long-term use
  - » involves dose accumulation
  - » e.g., phenacetin and interstitial nephritis
- Type D
  - » delayed effects (dose independent)
  - » carcinogenicity
  - » teratogenicity
  - » e.g., fetal hydantoin syndrome

Classification

- Types of allergic reactions
  - Type I - immediate, anaphylactic (IgE)
    - » e.g., anaphylaxis with penicillins
  - Type II - cytotoxic antibody (IgG, IgM)
    - » e.g., methyldopa and hemolytic anemia
  - Type III - serum sickness (IgG, IgM)
    - » antigen-antibody complex
    - » e.g., procainamide-induced lupus
  - Type IV - delayed hypersensitivity (T cell)
    - » e.g., contact dermatitis

Common Causes of ADRs

- Antibiotics
- Antineoplastics*
- Anticoagulants
- Cardiovascular drugs*
- Hypoglycemics
- Antihypertensives
- NSAID/Analgesics
- Diagnostic agents
- CNS drugs*

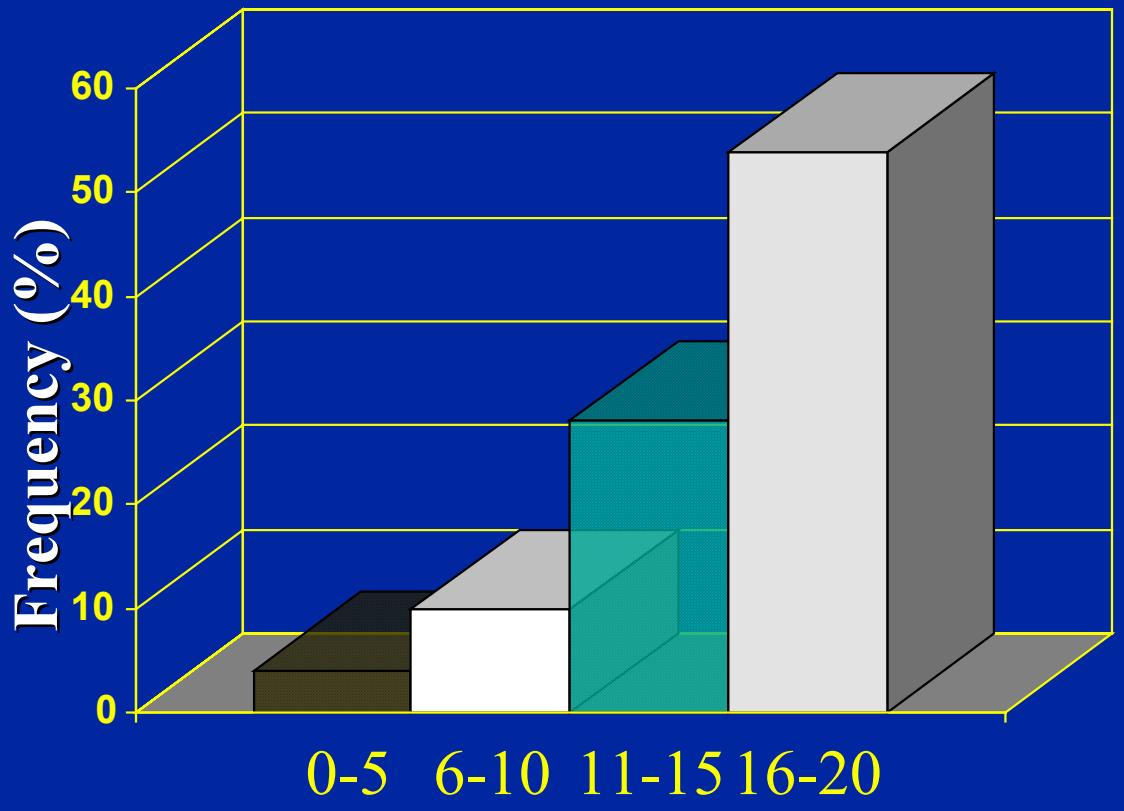
Body Systems Commonly Involved

- Hematologic
- CNS
- Dermatologic/Allergic
- Metabolic
- Cardiovascular
- Gastrointestinal
- Renal/Genitourinary
- Respiratory
- Sensory

ADR Risk Factors

- Age (children and elderly)
- Multiple medications
- Multiple co-morbid conditions
- Inappropriate medication prescribing, use, or monitoring
- End-organ dysfunction
- Altered physiology
- Prior history of ADRs
- Extent (dose) and duration of exposure
- Genetic predisposition

ADR Frequency by Drug Use



May FE. Clin Pharmacol Ther 1977;22:322-8

ADR Detection

- Subjective report
  - patient complaint
- Objective report:
  - direct observation of event
  - abnormal findings
    - » physical exam
    - » laboratory test
    - » diagnostic procedure

ADR Detection

- Medication order screening
  - abrupt medication discontinuation
  - abrupt dosage reduction
  - orders for tracer substances
  - orders for special tests or serum drug concentrations
- Spontaneous reporting
- Medication utilization review
  - Computerized screening
  - Chart review and concurrent audits

ADR Detection in Clinical Trials

- Methods
  - Standard laboratory tests
  - Diagnostic tests
  - Complete history and physical
  - Adverse drug event questionnaire
    - » Extensive checklist of symptoms categorized by body system
    - » Review-of-systems approach
    - » Qualitative and quantitative

ADR Detection in Clinical Trials

Limitations

- exposure limited to few individuals
  - » rare and unusual ADRs not detected
  - » 3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty
- exposure is often short-term
  - » latent ADRs missed
- external validity
  - » may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications

Preliminary Assessment

- Preliminary description of event:
  - Who, what, when, where, how?
  - What is the most likely causative agent?
  - How has event been managed thus far?
  - Is this an exacerbation of a pre-existing condition?
  - Alternative explanations/differential diagnosis
- Determination of urgency:
  - What is the patient's current clinical status?
  - How severe is the reaction?
- Appropriate triage:
  - Acute (ER, ICU, Poison Control)

Detailed Description of Event

- History of present illness
- Signs / Symptoms: PQRSTA
  - Provoking or palliative factors
  - Quality (character or intensity)
  - Response to treatment
  - Severity / extent
  - Temporal relationship (onset, duration, frequency)
  - Associated signs and symptoms

Pertinent Patient/Disease Factors

- **Demographics**
  - age, race, ethnicity, gender, height, weight
- **Medical history and physical exam**
  - Concurrent conditions or special circumstances
    - » e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding
  - Recent procedures or surgeries and any resultant complications
    - » e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

Pertinent Patient/Disease Factors

- End-organ function
- Review of systems
- Laboratory tests and diagnostics
- Social history
  - » tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures
- Pertinent family history
- Nutritional status
  - » special diets, malnutrition, weight loss

Pertinent Medication Factors

- Medication history
  - Prescription medications
  - Non-prescription medications
  - Alternative therapies
  - Medication use within previous 6 months
  - Allergies or intolerances
  - History of medication reactions
  - Adherence to prescribed regimens
  - Cumulative mediation dosages

Pertinent Medication Factors

- Medication
  - Indication, dose, diluent, volume
- Administration
  - Route, method, site, schedule, rate, duration
- Formulation
  - Pharmaceutical excipients
    - » e.g., colorings, flavorings, preservatives
  - Other components
    - » e.g., DEHP, latex

Pertinent Medication Factors

- Pharmacology
- Pharmacokinetics (LADME)
- Pharmacodynamics
- Adverse effect profiles
- Interactions
  - drug-drug
  - drug-nutrient
  - drug-lab test interference
- Cross-allergenicity or cross-reactivity

ADR Information

- Incidence and prevalence
- Mechanism and pathogenesis
- Clinical presentation and diagnosis
- Time course
- Dose relationship
- Reversibility
- Cross-reactivity/Cross-allergenicity
- Treatment and prognosis

ADR Information Resources

- Tertiary
  - » Reference books
    - – Medical and pharmacotherapy textbooks
    - – Package inserts, PDR, AHFS, USPDI
    - – Specialized ADR resources
      - Meyler's Side Effects of Drugs
      - Textbook of Adverse Drug Reactions
    - – Drug interactions resources
    - – Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)
  - » Review articles

ADR Information Resources

- Secondary
  - MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)
  - Excerpta Medica (Embase)
  - International Pharmaceutical Abstracts
  - Sedbase
  - Current Contents
  - Biological Abstracts (Biosis)
  - Science Citation Index
  - Clin-Alert and Reactions

ADR Information Resources

- Primary
  - » Spontaneous reports or unpublished data
    - – FDA
    - – Manufacturer
  - » Anecdotal and descriptive reports
    - – Case reports, case series
  - » Observational studies
    - – Case-control, cross-sectional, cohort
  - » Experimental and other studies
    - – Clinical trials
    - – Meta-analyses

Causality Assessment

- Prior reports of reaction
- Temporal relationship
- De-challenge
- Re-challenge
- Dose-response relationship
- Alternative etiologies
- Objective confirmation
- Past history of reaction to same or similar medication

Causality Assessment

- Examples of causality algorithms
  - Kramer
  - Naranjo and Jones
- Causality outcomes
  - Highly probable
  - Probable
  - Possible
  - Doubtful

Naranjo ADR Probability Scale

Naranjo CA. Clin Pharmacol Ther 1981;30:239-45

To assess the adverse drug reaction, please answer the following questionnaire and give the patient a score.

		Yes	No	Do Not Know	Score
1.	Are there previous conclusive reports on this reaction?	+1	0	0	____
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	____
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	____
4.	Did the adverse reactions appear when the drug was readministered?	+2	-1	0	____
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	____
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	____
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	____
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	____
9.	Did the patient have a similar reaction to the same or similar drug in *any* previous exposure?	+1	0	0	____
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	____
				Total Score	____

Total Score	*ADR Probability Classification*
9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Management Options

- Discontinue the offending agent if:
  - » it can be safely stopped
  - » the event is life-threatening or intolerable
  - » there is a reasonable alternative
  - » continuing the medication will further exacerbate the patient's condition
- Continue the medication (modified as needed) if:
  - » it is medically necessary
  - » there is no reasonable alternative
  - » the problem is mild and will resolve with time

Management Options

- Discontinue non-essential medications
- Administer appropriate treatment
  - » e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytonadione, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon
- Provide supportive or palliative care
  - » e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics
- Consider rechallenge or desensitization

Follow-up and Re-evaluation

- Patient's progress
- Course of event
- Delayed reactions
- Response to treatment
- Specific monitoring parameters

Documentation and Reporting

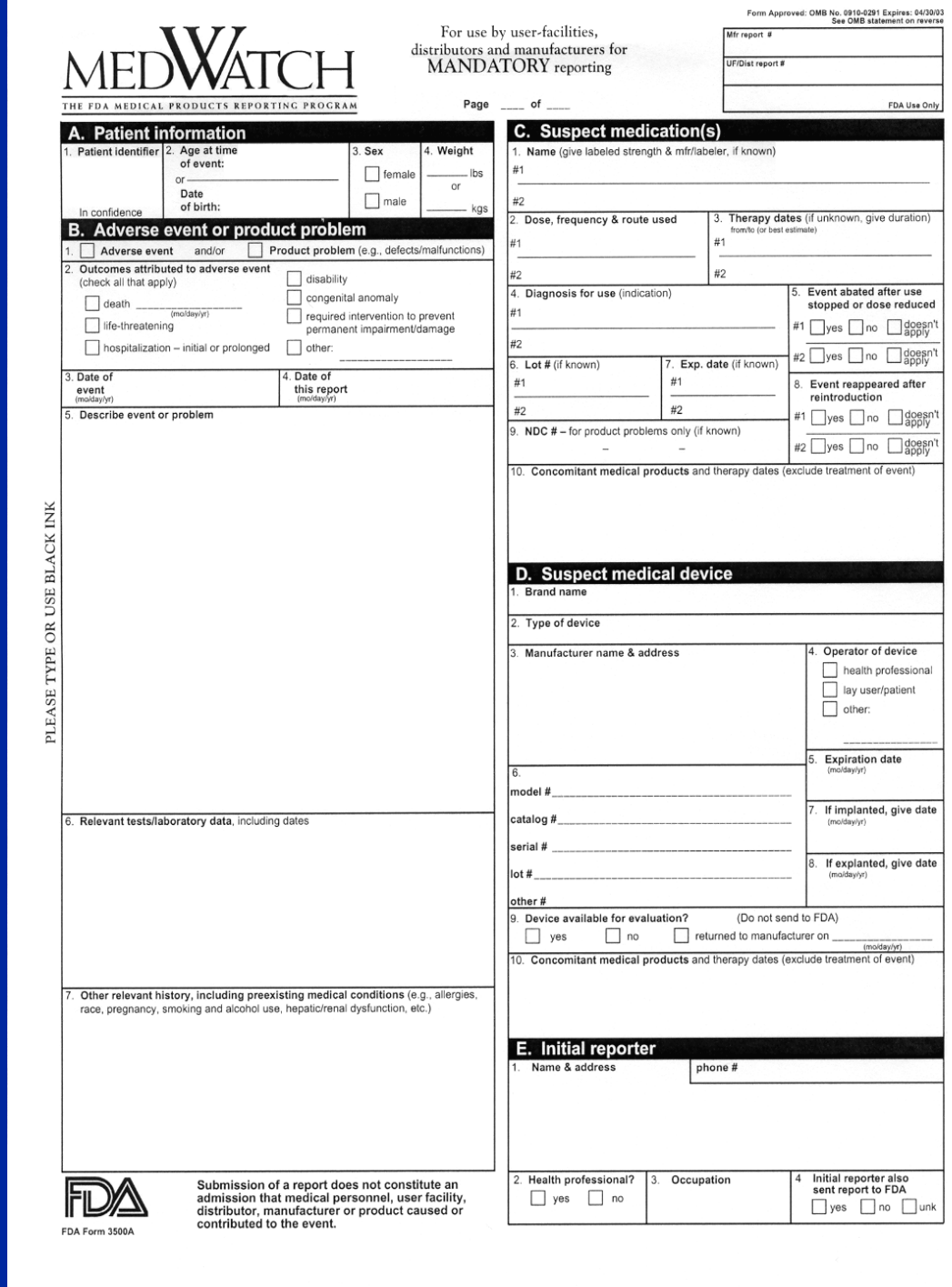
- Medical record
  - Description
  - Management
  - Outcome
- Reporting responsibility
  - JCAHO-mandated reporting programs
  - Food and Drug Administration
    - » post-marketing surveillance
    - » particular interest in serious reactions involving new chemical entities
  - Pharmaceutical manufacturers
  - Publishing in the medical literature

Components of an ADR Report

- Product name and manufacturer
- Patient demographics
- Description of adverse event and outcome
- Date of onset
- Drug start and stop dates/times
- Dose, frequency, and method
- Relevant lab test results or other objective evidence
- De-challenge and re-challenge information
- Confounding variables

MEDWATCH 3500A Reporting Form

https://www.accessdata.fda.gov/scripts/medwatch



Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr report #
UF/Dist report #
FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: / or Date of birth:
3. Sex: female / male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - death ____ (mo/day/yr)
   - life-threatening
   - hospitalization – initial or prolonged
   - disability
   - congenital anomaly
   - required intervention to prevent permanent impairment/damage
   - other: ____
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 / #2
2. Dose, frequency & route used #1 / #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 / #2
4. Diagnosis for use (indication) #1 / #2
5. Event abated after use stopped or dose reduced #1 yes no doesn't apply / #2 yes no doesn't apply
6. Lot # (if known) #1 / #2
7. Exp. date (if known) #1 / #2
8. Event reappeared after reintroduction #1 yes no doesn't apply / #2 yes no doesn't apply
9. NDC # – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device: health professional / lay user/patient / other: ____
5. Expiration date (mo/day/yr)
6. model # ____ catalog # ____ serial # ____ lot # ____ other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) yes no returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address
   phone #
2. Health professional? yes no
3. Occupation
4. Initial reporter also sent report to FDA yes no unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.